Remarks

Claims 84-85, 89-93 and 95-102 are pending following entry of the claim amendments submitted above. Claims 1-3, 5-8, 11, 12, 15-83 and 94 have been canceled. Claim 86 has been rewritten in independent form as new Claim 95. Claims 87 and 88 have been rewritten as new Claims 96 and 97 to depend from new Claim 95. New Claims 98-102 depend from Claim 95 and are analogous to Claims 89-93, which depend from Claim 84.

These amendments are presented to more particularly point out the features of the present invention, and to put the claims in better condition for allowance or for consideration on appeal. The remaining issues in this application are discussed below.

I. Interview Summary.

Applicants wish to express their appreciation to the Examiner for the time and courtesy extended toward Applicants' representative during the telephonic interview on July 17, 2001. During the telephonic interview, the outstanding obviousness rejection over Johnston et al. and Falo et al. was discussed. In particular, Applicants discussed data showing protection against cancer with alphavirus vectors expressing a native cancer antigen (the data presented in the Olmsted Declaration, submitted concurrently herewith). The Examiner indicated that she was favorably disposed towards claims reciting a "native cancer antigen," but requested that further clarification of Falo et al. be provided with respect to these claims.

II. The Claims are Patentable over Johnston et al. in view of Falo et al.

Claims 1-3, 5-8, 11, 12, 15, 16, and 84-94 stand rejected under 35 U.S.C. § 103 (a) as being unpatentable as obvious over Johnston et al. in view of Falo et al. This is the sole rejection remaining in this application. Claims 1-3, 5-8, 11, 12, 15, 16 and 94, which recite artificial tumor antigens, have been canceled. Although Applicants disagree with the outstanding rejection as applied to these claims, these claims have been canceled from the present application in order to expedite the

prosecution of this application to allowance in accordance with the USPTO Patent Business Goals (65 Fed. Reg. 54603, September 8, 2000).

The outstanding rejection will be discussed below with respect to pending Claims 84-85, 89-93 and 95-102, which recite native cancer antigens.

A. Legal Standards for Obviousness.

The Patent Office has the initial burden under §103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071 , 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). The Applicants respectfully note that in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all of the claim limitations (MPEP § 706.02(j)). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Federal Circuit has articulated the following legal test for obviousness: "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. . . . Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) (emphasis added). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. *In re Geiger*, 2 USPQ2d 1276 (CAFC 1987). The mere fact that references can be combined does not render the combination obvious unless the prior art also suggests the desirability of the combination. *In re Fritch*, 23 USPQ 2d 1780 (CAFC 1992). The Court of Appeals for the Federal Circuit has addressed this issue and has stated that "[t]he mere fact that

the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." *In re Gordon*, 221 USPQ, 1125, 1127 (Fed. Cir. 1985) (emphasis added).

The Applicants respectfully contend that the Patent Office has failed to establish a *prima facie case* of obviousness in the present case.

B. The Claimed Compositions are not Obvious over the Cited References.

The Final Action states that "applicant is referred to Johnston et al. for the teaching of the alphavirus vector to deliver an antigen and to Falo et al. for the teaching of the artificial cancer antigen. The combination of the references thus teaches the claimed vectors and methods" (Final Action; page 3, final paragraph).

Applicants' respectfully disagree. First, the cited references are not properly combined to arrive at the present invention. The references are not properly combined because the references themselves do not provide a motivation or suggestion to combine. Moreover, the desirability of the combination is not taught by the cited references. It is conceded in the previous Office Action that Johnston et al. does not disclose an alphavirus vector encoding a native cancer antigen (Office Action of October 18, 2000, page 9, lines 3-5). Likewise, this suggestion is not found in Falo et al.

Further, even if the teachings of the cited references are combined, one of ordinary skill in the art would not arrive at the claimed invention. The present claims recite an alphavirus vector encoding a "native cancer antigen." Neither of the cited references, considered alone or together, provide any teaching or suggestion regarding the claimed vectors encoding a native cancer antigen.

The Final Action states:

> Absent some evidence to the contrary, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation that an artificial cancer antigen delivered via an alphavirus vector would have provided an effective prophylactic and therapeutic method of anti-tumor immunization because Falo et al. specifically teaches the effectiveness of cells tagged with an artificial cancer antigen and Johnston et al. teaches alphavirus vectors for effective intracellular delivery of an antigen to cells.

(Final Action, page 4, lines 8-14; emphasis added; citations omitted). Applicants respectfully submit that, even if the quoted statement from the Final Action is accepted as true, it would not render the subject matter of pending Claims 84-85, 89-93 and 95-102 obvious.

C. Unexpected Properties of the Claimed Compositions.

Falo et al. describes a two-part vaccination strategy comprising a first immunization with a particulate iron-ovalbumin (an artificial tumor antigen) vaccine, followed by a second immunization with tumor cells that have been genetically modified *ex vivo* to express the ovalbumin antigen so as to induce an immune response against the modified tumor cells (*see*, Falo et al., Section 7, Example, pages 23-25). The initial immunization may also be carried out with peptide pulsed (ovalbumin) dendritic cells, which are then introduced into the subject to induce an immune response against the ovalbumin antigen (*see*, Falo et al., Section 8, Example, pages 26-29). Falo et al. further discloses that administration of B16 tumor cells modified to express ovalbumin alone is ineffective in inducing an immune response against the tumor (Falo et al., page 22, lines 2-5). In sum, Falo et al. discloses a two-step protocol to achieve an immune response against tumor cells (*see, e.g.*, page 8, lines 3-5).

As an initial matter, Applicants note that the present claims do not recite an artificial tumor antigen, but rather a "native cancer antigen." Falo et al. is exclusively concerned with artificial tumor antigens. For example, Falo et al. clearly states that "[a]t the core of the invention are anti-tumor immunization methods based on cross-priming a mammalian host to natural MHC class I restricted tumor antigens with an artificial tumor antigen (ATA)" (page 1, lines 21-23; emphasis added).

Moreover, the Final Action appears to state that the presently-claimed composition is obvious because Johnston et al. teaches that an alphavirus vector may be used to deliver a nucleotide sequence encoding an artificial tumor antigen to a cell, which may then be administered in the secondary immunization according to

Falo et al. Again, even if accepted as true, it would not render the presently-claimed invention obvious.

The claimed compositions comprise an alphavirus vector encoding a native cancer antigen which may be directly administered to a subject to achieve a prophylactic and/or therapeutic effect against cancer, including tumor-forming cancers. Using the inventive alphavirus particles, it is not necessary to use a two-step protocol or an artificial tumor antigen as taught by Falo et al. to achieve a prophylactic and/or therapeutic immune response against cancer (*see*, Specification, page 17 line 1 to page 18 line 4).

To illustrate, the **Rule 132 Declaration of Robert M. Olmsted pursuant to 37 C.F.R. § 1.132** (*hereinafter*, "the Olmsted Declaration") submitted herewith demonstrates protection against tumor cells developed from a tumorigenic and metastatic mammary tumor (stably transformed to express the HER2/*neu* gene) is achieved with an alphavirus replicon vector expressing the rat HER2/*neu* gene according to the present invention. Mice were injected in the foot pad with an alphavirus replicon vector encoding the influenza hemagglutinin gene (negative control) or with one of two doses of the alphavirus replicon vector encoding the rat HER2/*neu* gene at three different time points, *i.e.*, days 0, 14 and 21 (Olmsted Declaration; para. 2). On day 35 after commencement of the immunization protocol, the mice were injected in the mammary fat pad with tumor cells. In control mice, 7/8 mice developed tumors. In contrast, only 1/16 treated mice developed any tumors (Olmsted Declaration; para. 3). Further analysis demonstrated that the treated animals, but not controls, were strongly seropositive for the rat *neu* gene product (Olmsted Declaration; para. 3).

These results indicate that alphavirus vectors provide protection against tumor induction in a model mouse system (Olmsted Declaration; para. 4).

It would not have been obvious to one of ordinary skill in the art at the time of invention that a protective immune response against cancer can be provided by immunization with an alphavirus vector. The requisite motivation is certainly not provided by Johnston et al. or Falo et al., considered alone or in combination. It is known in the art that the induction of an effective immune response against native

cancer antigens has been problematic. In particular, it appears that native cancer antigens are only poorly immunogenic, if at all, because the cancer antigens are not recognized as foreign by the immune system, *i.e.*, the animal has tolerance to the cancer antigen.

Accordingly, it would have been unexpected to one of ordinary skill in the art that a composition comprising an alphavirus vector encoding a native cancer antigen could be directly administered to an animal to effectively provide protection against cancer (including tumors) as demonstrated by the Olmsted Declaration. Thus, the claimed compositions are not obvious in view of the cited references.

During the telephonic interview of July 17, 2001, the teachings of Falo et al. regarding cancer antigens were discussed. On page 7, lines 4-10, Falo et al. discusses the use of a "tumor rejection antigen," including MAGE-1, MAGE 3, Melan-A, gp100, p53, CEA and HER2/neu, as an artificial tumor antigen (*see also*, Falo et al. at page 16, lines 20-26). The teachings of Falo et al. are somewhat unclear in this regard. Nonetheless, the presently-claimed invention may be readily distinguished therefrom. First, Falo et al. is intending to use these "tumor rejection antigens" as artificial tumor antigens, presumably to produce an immune response against tumors that do not express these antigens. Second, Falo et al. discloses use of these tumor rejection antigens in the two-part vaccination strategy discussed above, as for any other artificial tumor antigen. Falo et al. does not disclose or suggest that protection against cancer or tumors may be achieved by simply immunizing with the "tumor rejection antigen."

Accordingly, Applicants' have demonstrated unexpected properties of the presently-claimed alphavirus vectors expressing a native cancer antigen, *i.e.*, these compositions may be administered directly to a subject to achieve protection against cancer (including tumors) without the use of an artificial tumor antigen, as disclosed by Falo et al. These unexpected characteristics of the claimed compositions are not disclosed or suggested by Falo et al., taken alone or in combination with Johnston et al.

In view of the foregoing discussion, it is respectfully submitted that the subject matter of Claims 84-85, 89-93 and 95-102 is not rendered obvious by Johnston et al.

in view of Falo et al. Accordingly, Applicants respectfully request that the outstanding rejection on this basis be withdrawn.

III. Conclusion.

The points and concerns raised by the Examiner having been addressed in full, it is respectfully submitted that this application is in condition for allowance, which action is respectfully requested. Should the Examiner have any remaining concerns, it is respectfully requested that the Examiner contact the undersigned attorney to expedite the prosecution of this application.

Respectfully submitted,

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Customer Number:

20792
PATENT TRADEMARK OFFICE

Enclosure: Rule 132 Declaration of Robert M. Olmsted

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on July 26, 2001

Traci A. Brown
Date of Signature: July 26, 2001

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